

REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 1, 5-7, 19-22, 24-29 and 31 are pending after entry of the amendments above.

Claims 1, 5-7 and 19-31 were rejected. No claims were allowed.

Claims 23 and 30 are canceled without prejudice.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

No new matter has been added.

Request for Withdrawal of Finality

Applicants respectfully request withdrawal of the finality of the Office Action.

The Office Action at page 5 states that all claims were drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR §1.129(a), and could have been entered in the application prior to entry under 37 CFR §1.129(a).

Applicants respectfully note that the prior submission was not under 37 CFR §1.129(a); in fact, the application is not entitled to take advantage of this rule.

Rather, the prior submission on July 3, 2002 was a Request for Continued Examination (RCE).

The RCE was filed as a result of the Advisory Action mailed April 11, 2002, in which the Office indicated that exhibits submitted with the Response to the Final Office Action (mailed April 3, 2002) would NOT be considered. These exhibits were, in applicants view, evidence of patentability. This evidence was not considered.

37 C.F.R. §1.114(c) requires that a Request for Continued Examination include a "submission." As set out in this rule, a "submission" can be "new evidence of patentability."¹

¹ 37 C.F.R. §1.114 Request for continued examination.

(c)A submission as used in this section includes, but is not limited to, an information disclosure statement, an amendment to the written description, claims, or drawings, new arguments, or new evidence in support of patentability. If reply to an Office

In addition, applicants filed a Supplemental Amendment on August 9, 2002, which amendment presented new claims for the Examiner's consideration.

As noted in 37 C.F.R. §1.114(c), exhibits are "new evidence of patentability" and thus qualify as a "submission". Because these exhibits had not been considered, they remained "new evidence of patentability." Thus, withdrawal of the finality of the present Office Action is appropriate.

Rejections under §101 and §112, ¶1

Claims 1, 5-7 and 19-31 were rejected under §§101 and 112, ¶1 on the grounds that the claimed invention has no apparent or disclosed specific and substantial credible utility. This rejection is respectfully traversed.

Review of the Statutory Utility Requirement

The statutory requirements for utility are summarized in the MPEP §2107, which summarizes the law as follows:

An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

The MPEP §2107 further states that:

(1) If the applicant has asserted that the claimed invention is useful *for any particular practical purpose* (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(i) A claimed invention must have a specific and substantial utility. This requirement excludes "throw-away," "insubstantial," or "nonspecific" utilities, such as the use of a complex invention as landfill, as a way of satisfying the utility requirement of 35 U.S.C. 101.

(ii) *Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (e.g., test data, affidavits or declarations from experts in the art, patents or printed publications)* that is probative of the applicant's assertions. An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement. (emphasis added)

MPEP §2107 further states:

Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, *unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement*. Similarly, *Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered*.

Once a *prima facie* showing of no specific and substantial credible utility has been properly established, the applicant bears the burden of rebutting it. The applicant can do this by amending the claims, by providing reasoning or arguments, *or by providing evidence in the form of a declaration under 37 CFR 1.132 or a patent or a printed publication that rebuts the basis or logic of the prima facie showing*. If the applicant responds to the *prima facie* rejection, the Office personnel should review the original disclosure, any evidence relied upon in establishing the *prima facie* showing, any claim amendments, and any new reasoning or evidence provided by the applicant in support of an asserted specific and substantial credible utility. It is essential for Office personnel to recognize, fully consider and respond to each substantive element of any response to a rejection based on lack of utility. *Only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained*. (emphasis added)

Thus the Office is required to accept an asserted utility where the utility is specific and substantial, as well as credible as determined from the perspective of the ordinarily skilled artisan and all evidence of record.

Here the asserted utility is both specific and substantial – use as a tumor marker is not a “throw-away”.

Furthermore, applicants have asserted a credible utility based on the reasoning set out in the specification, which reasoning is supported by evidence in the form of post-filing publications.

These points are discussed in more detail below.

The Asserted Utility

As discussed in the prior response, the specification asserts that the 2.2412 protein and its encoding DNA are useful as a tumor marker. This asserted utility is based on the following set out in the specification:

- 1) **2.2412 protein is an effector protein for the Grb7 family of signalling proteins (i.e., a protein that specifically binds to a signaling protein to facilitate a signal transduction cascade)**
 - a) **2.2412 protein specifically binds Grb14 and specifically binds Grb7 (specification page 10, line 26 to page 11, line 32)**
 - b) **binding of 2.2412 protein to Grb14 requires the N-terminal region of Grb14, which contains highly conserved proline-rich motif thought to mediate interaction of the Grb7 family of proteins with their effectors (specification page 11, lines 29-32)**
 - c) **2.2412 contains multiple ankyrin repeats, which are known to have a role in protein-protein interactions (specification page 9, lines 25-34)**
- 2) **Grb7 family members are signal transduction molecules that exhibit differential expression in certain human cancers (particularly breast cancer) (specification page 5, lines 13-15). Specifically, at the time of filing**
 - a) **Grb7 family members were known to be associated with oesophageal carcinoma,² primary gastric cancer,³ and breast cancer.⁴**
 - i) **Grb14 was known to be differentially expressed in breast cancer⁵**
 - ii) **Grb7 was known to be differentially expressed in breast cancer⁶**
- 3) **Given that 2.2412 specifically binds Grb14 and Grb7 which were known to be differentially expressed in cancer cells compared to normal cells, it is reasonable to conclude that effectors for these proteins such as 2.2412 will also be differentially expressed (specification page 5, lines 13-16).**
- 4) **The specification thus sets out a credible association of 2.2412 expression and human cancers**

In order to rebut the Office's position that the asserted utility of 2.2412 as a tumor marker is not credible, applicants previously noted that 2.2412, now referred to in the art as Tankyrase2⁷ is in fact tumor marker. Specifically, Tankyrase2 is a tumor-specific antigen as evidenced by detection of anti-

² Tanaka et al. 1997 Cancer Res. 57:28-31.

³ Kishi et al. 1997 Biochem Biophys. Res. Commn. 232:5-9.

⁴ Stein et al. 1994 EMBO J 13:1331-40.

⁵ Daly et al. 1996 J. Biol. Chem. 271:12502-10.

⁶ Stein et al. 1994 EMBO J 13:1331-40

⁷ Lyons et al. 2001 J. Biol. Chem. 276:17172-80.

Tankyrase2 antibodies in sera of breast cancer patients⁸ and in sera of patients having meningioma.⁹

This evidence in the form of post-filing publications supports the utility asserted in the specification, and serves to rebut the Office's rejections based on a lack of a specific, substantial, and credible utility as summarized in MPEP §2107 (see above).

Applicants respectfully disagree with the Office's position that because the specification provides data showing that 2.2412 is expressed in all tissues examined except kidney cells "one skilled in the art would reasonably conclude that the novel polypeptide 2.2412 cannot possibly be a specific marker for any cancer cells due to the general pattern of its tissue distribution.

As noted above, both Grb14 and Grb7 are differentially expressed in breast cancer, respectively. In fact, each of Grb14 and Grb7 are increased in expression in these cancerous cells compared to normal cells.

Applicants respectfully submit that one would reasonably expect that expression of 2.2412 would also be differentially expressed, and that such expression would be different between normal and cancerous cells of the same tissue origin. Detection of expression of 2.2412 in a broad range of tissues does not undermine this position – the relevant comparison is between normal cells and cancerous cells of the same tissue type.

Additional Evidence – Dr. Hitoshi's Declaration under 37 C.F.R. §1.132

Notwithstanding this argument, applicants provide herewith still further evidence, in the form of a declaration by Dr. Yasumichi Hitoshi under 37 C.F.R. §1.132, that 1) the asserted utility as set out in the specification as filed is credible to the ordinarily skilled artisan; and 2) additional data showing the 2.2412 is differentially expressed in cancerous human cells relative to normal human cells.

After reviewing the instant specification, Dr. Hitoshi declares that one of ordinary skill in the relevant field would find the assertion that 2.2412 (Tankyrase2) is a tumor marker to be credible in view of:

- 1) **The evidence that the 2.2412 protein is an effector protein for the Grb7 family of signalling proteins** (i.e., a protein that specifically binds to a signaling protein to facilitate a signal transduction cascade), which evidence included the showing the specification that:

⁸ Kuimov et al., 2001 Genes Immun. 2:52-5.

⁹ Monz et al., 2001 Clin. Cancer Res. 7:113-9.

- a) **2.2412 protein specifically binds Grb14 and specifically binds Grb7** (specification page 10, line 26 to page 11, line 32)
- b) **binding of 2.2412 protein to Grb14 requires the N-terminal region of Grb14, which contains highly conserved proline-rich motif thought to mediate interaction of the Grb7 family of proteins with their effectors** (specification page 11, lines 29-32)
- c) **2.2412 contains multiple ankyrin repeats, which are known to have a role in protein-protein interactions** (specification page 9, lines 25-34)
- 2) **The knowledge at the time the application was filed that Grb7 family members are signal transduction molecules that exhibit differential expression in certain human cancers (particularly breast cancer)** (specification page 5, lines 13-15). Specifically, that at the time of filing
 - a) Grb7 family members were known to be associated with oesophageal carcinoma,¹⁰ primary gastric cancer,¹¹ and breast cancer.¹²
 - i) **Grb14 was known to be differentially expressed in breast cancer**¹³
 - ii) **Grb7 was known to be differentially expressed in breast cancer**¹⁴
- 3) **Given that 2.2412 specifically binds Grb14 and Grb7 which were known to be differentially expressed in cancer cells compared to normal cells, it is reasonable to conclude that effectors for these proteins such as 2.2412 will also be differentially expressed** (specification page 5, lines 13-16).
- 4) **The specification supports a credible association of 2.2412 expression and human cancers.**

In addition, Dr. Hitoshi provides further evidence that 2.2412 is a tumor marker by showing that 2.2412 (Tankyrase2) is in fact differentially expressed in human cancer cells compared to normal human cells. Thus, the asserted utility of 2.2412 as a tumor marker is in fact credible.

¹⁰ Tanaka et al. 1997 Cancer Res. 57:28-31.

¹¹ Kishi et al. 1997 Biochem Biophys. Res. Commun. 232:5-9.

¹² Stein et al. 1994 EMBO J 13:1331-40.

¹³ Daly et al. 1996 J. Biol. Chem 271:12502-10.

¹⁴ Stein et al. 1994 EMBO J 13:1331-40

Conclusion

Applicants have provided more than ample evidence that the asserted utility is credible based on the disclosure in the specification and the knowledge at the time of filing. Applicants have provided even further evidence—in the form of post-filing publications and Dr. Hitoshi's declaration – that the asserted utility is credible. As best stated in MPEP §2107:

Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, *unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement*. Similarly, *Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered*.

The Examiner is thus respectfully requested to withdraw the rejections under both §101 and §112, ¶1.

Rejection under §112, ¶1 - Written Description

Claims 1, 5-7, 20, 22-28 and 30 were rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey to the skilled artisan that the inventors had, when the application was filed, possession of the claimed invention. This rejection is respectfully traversed as applied and as it maybe applied to the pending claims.

Applicants submit that the disclosure adequately describes the polynucleotides as claimed. The specification not only provides the DNA and amino acid sequence of 2.2412, but it also further characterizes the protein as containing multiple ankyrin repeats (see Fig. 1), which are known to play a role in protein-protein interactions. Thus, the specification provides both structural and functional information about the claimed polynucleotide. The claims reflect this function in that they recite that the claimed polynucleotide encodes an effector of the Grb7 family of signalling proteins. [NOTE: **Consider amending to recite specifically binds Grb14 and/or specifically binds Grb7? Your thoughts are appreciated.**]

These points notwithstanding, the claims are amended to recite that the claimed polynucleotide have at least 95% sequence identity to the amino acid sequence of SEQ ID NO:2. (claim 1) or 95% sequence identity to the nucleotide sequence of SEQ ID NO:1 (claim 22).

Applicants note that specifications having disclosure similar to that of the instant application have been deemed by the Office to support claims of such scope. Several patents have issued as recently as January 2003 with claims reciting 95% sequence identity (see, e.g., U.S. Pat. No. 6,509,448). Other exemplary patents that have issued with such sequence identify language include U.S. Pat. Nos. 6,156,540; 6,506,587; 6,504,009; 6,503,733; 6,503,700; and 6,500,635. A search of the USPTO full-text database using the search strategy [aclm/sequence and aclm/identity and (aclm/amino or aclm/protein or aclm/polypeptide) and (aclm/75 or aclm/80 or aclm/85 or aclm/90 or aclm/95)] identified over 90 issued US patents, 26 of which have issued since 2002.

Applicants respectfully request withdrawal of this rejection

Conclusion

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number RICE-012.

Respectfully submitted,
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Enclosures: Declaration Under 37 C.F.R. §1.132 by Yasumichi Hitoshi, Ph.D.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The claims are amended herein as shown below. Deleted text is indicated by strikethrough.

Added text is indicated by bold and underlining.

Claims 1 and 22 are amended.

Claims 23 and 30 are canceled without prejudice.

1. **(Thrice Amended)** An isolated polynucleotide molecule encoding an effector protein for the Grb7 family of signalling proteins, wherein the polynucleotide molecule comprises a nucleotide sequence encoding an amino acid sequence having at least **95%** ~~85%~~ sequence identity to the amino acid sequence as shown in SEQ ID NO:2.

22. **(Amended)** An isolated polynucleotide molecule encoding an effector protein for the Grb7 family of signalling proteins, wherein the polynucleotide molecule comprises a nucleotide sequence having at least **95%** ~~85%~~ sequence identity to that shown in SEQ ID NO:1.